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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,575	11/28/2000	Dale B. Schenk	15270J-005912US	6096

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	17

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,575	SCHENK, DALE B.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) *1-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-19 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 12 14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The Amendments filed 15 May 2003 (Paper No. 11) and 21 May 2003 (Paper No. 16) have been entered in full. Claims 11-13 and 21-25 have been amended. Claims 20 and 26-57 have been cancelled. Claims 1-10 remain withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected material, there being no allowable generic or linking claim. Claims 11-19 and 21-25 are under examination.

2. The Applicant's continued traversal of the Restriction requirement as set forth in Office Action Paper No. 6 (27 March 2002) is noted and maintained for the reasons as set forth in Office Action Paper No. 9 (21 November 2002).

3. The information disclosure statement filed 11 December 2001 (Paper No. 6) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP §609 because citations #144, #162, #174, and #186 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because they do not have publication dates. A copy of citation #187 was not present in the file. They have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

4. The Applicant has requested that the double patenting rejections be held in abeyance until indication of allowability in the instant application. The Examiner *accepts* this and herein

indicates whether or not the rejections under double patenting as set forth at pp. 10-13 ¶20-28 in the previous Office Action (Paper No. 9, 21 November 2002) have been *obviated* by amendment and if not, has maintained them where appropriate.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

6. The objection to the specification as set forth at pp. 3-4 ¶5-6 of the previous Office Action (Paper No. 9, 21 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 16, 21 May 2003).

7. The objection to the drawings as set forth at pp. 4 ¶7 of the previous Office Action (Paper No. 9, 21 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 16, 21 May 2003).

8. The rejection of claims 11-25 under 35 U.S.C. §101 (double patenting) as set forth at pp. 11 ¶24-25 of the previous Office Action (Paper No. 9, 21 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 16, 21 May 2003).

9. The rejection of claims 11-25 under 35 U.S.C. §112 ¶1 as set forth at pp. 11 ¶24-25 of the previous Office Action (Paper No. 9, 21 November 2002) is *withdrawn in part* in view of Applicant's amendments (Paper No. 16, 21 May 2003).

Maintained Objections And/Or Rejections

10. The objection to claims **13, 15,** and **16** as set forth at pp. 5 ¶8 of the previous Office Action (Paper No. 9, 21 November 2002) is *maintained.* Until a descision is reached concerning the Applicant's petition, claims 13, 15, and 16 contain unelected material. The restriction requirement is still in effect and therefore the objection is maintained.

11. Claims **11-19** and **21-25** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons as set forth in at pp. 5-10 ¶9-19 of the previous Office Action (Paper No. 9, 21 November 2002).

12. The Applicant traverses the 35 U.S.C. §112 ¶1 rejection of claims **11-19** and **21-25** as set forth in at pp. 5-10 ¶9-19 of the previous Office Action (Paper No. 9, 21 November 2002) on the following grounds: **(a)** the PDAPP mouse model is a good mouse model for Alzheimer's disease, **(b)** $A\beta_{42}$ administration, for both active {reference to Sigurdsson *et al.* (2002)} and active {reference to Sigurdsson *et al.* (2003)} immunization protocols, is representative of PrP and synuclein, **(c)** adequate guidance is presented to practice the invention for Aβ immunization is predictive of ATTR immunization, **(d)** it is not necessary to fully understand all the cellular and humoral effects of ATTR to practice in the invention, **(e)** citing *In re Brana* (Fed. Cir. 1995) the Applicant argues that the USPTO is not responsible for testing therapies, **(f)** the mutations claimed are known in the art, **(g)** Tanaka's study was done without adjuvant, **(h)** the Smith and Weissman reference does not include use of an adjuvant, **(i)** a nexus between active and passive

immunization is present for prion diseases. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

13. The instant claims are drawn very broadly to a method of treating a disorder characterized by amyloid deposition in mammalian subject via active immunization with ATTR. The language of said claims encompasses both *treatment* and *prevention* said disorders which covers a broad range of disorders {see Sipe (1992) "Amyloidosis" Annu. Rev. Biochem. **61**: 947-975}.

14. The specification teaches that the administration of particular $A\beta_{42}$ (AN1792) fragments with an immunogenic adjuvant reduces β-amyloid levels within the brains of transgenic PDAPP mice. These mice exhibit Alzheimer type over production and build up of β-amyloid within the brain [Chapman (21/28 December 2000) "Model Behavior." Nature **408**: 915-916]. However, administration of $A\beta_{42}$ to Alzheimer's patients is not predictive of how administration of ATTR affects patients with all amyloid diseases or any given amyloid dependent disorders. There are no examples directed to ATTR, diseases caused by ATTR, or art-accepted ATTR animal models.

15. Since the specification fails to provide any guidance for the successful prevention of ATTR amyloid disorders via active immunization, and since resolution of the various complications in regards to treating amyloid diseases and disorders is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known ATTR protein fragments, amyloid disorder signs and symptoms to correlate with prevention of

said amyloid disorder. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

16. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed method of using ATTR for active immunization in a patient to prevent all amyloid disorders. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed method for prevention, such a disclosure would not be considered enabling since the state of amyloid disorders is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

17. On "**(a)**", the Examiner *accepts* the Applicant's argument. The PDAPP mouse is a representative mouse model of Alzheimer's disease [see Chapman (21/28 December 2000) "Model Behavior." Nature **408**: 915-916]. However, the instant claims, as amended, are directed to amyloid disorders involving transthyretin of which the PDAPP mouse is not an adequate model.

18. In response to "**(b)**", the Examiner acknowledges that amyloid proteins share some structural characteristics, however, this is insufficient to predict the immunological effects of immunization of one amyloid protein component with another. It is further noted that the PrP

results were obtained using a prion disease animal model. Sigurdsson *et al.* (July 2002) "Immunization Delays the Onset of Prion Disease in Mice." American Journal of Pathology **161**(1): 13-17 and Sigurdsson *et al.* (2003) "Anti-prion antibodies for prophylaxis following prion exposure in mice." Neuroscience Letters **336**: 185-187 offer support for use of active and passive immunization as a means of treatment for prion disease however, neither study shows prevention of prion diseases or discusses the treatment of transthyretin disorders.

19. In light of the breadth of the claims, "Prevention" is understood in the art to mean a total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. In fact, Sigurdsson et al. (July 2002) teaches:

> "Although neither of our treatment paradigms prevented prion disease, the close correlation between antibody levels and incubation time shows the promise of vaccination therapy for this untreatable and fatal neurodegenerative disease. Overall, the vaccination-mediated delay in the onset of prion disease is highly reproducible, correlates well with antibody titer, with the best therapeutic effect being obtained in mice preimmunized before infection." (pp. 15)

While the specification demonstrates a level of relief from symptoms using Aβ as an immunogen in mice and Applicant has provided compelling evidence to support the claimed method as a therapeutic method, total prevention was not achieved.

20. Concerning "**(c)**", the Examiner *accepts* the Applicant's argument in regards to use of Ab or PrP as an immunogen but the instant application is drawn to use of ATTR, a fragment of transthyretin. In further regards, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of

computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly small peptides, conjugation appears to be required for promoting an effective immune response.

21. On "**(d)**", the Examiner *accepts* the Applicant's argument. However, the cautions of using a non-ATTR amyloid protein as predictive of ATTR immunization is not accepted for the reasons discussed above. Furthermore Palha *et al.* (2001) "Antibody recognition of amyloidogenic transthyretin variants in serum of patients with familial amylodiotic polyneuropathy." J. Mol. Med. **78**: 703-707 teaches the characterization of a monoclonal antibody that will bind transthyretin (TTR) variants which are amyloidogenic but not others (Table 1; pp. 707). Thus it is not clear to the skilled artisan whether or not ATTR fragments which elicited this antibody or any other would be "therapeutic" since antibodies with differing selectivity can be made.

22. To address "**(e)**", the Examiner *accepts* the Applicant's argument that the USPTO is not responsible for testing the effectiveness of PrP immunizations. However, as Sigurdsson *et al.* (2003) teaches:

> "Although indicating the promise of immunologically-based therapy for prion disease, these prior studies were not designated to demonstrate the clinical relevance of prion-related immunization paradigms. It is also well known that PrP^{Sc} content does not necessarily correlate with disease progression." (pp. 186)

Taken into consideration, the Examiner accepts that the post-filing references provide guidance for treatment but not prevention or assurance of success with human patients.

23. In response to "**(f)**", the Examiner *maintains* the rejection that Aβ and PrP are not predictive of one another. The post-filing references used Ab in an Alzhimer's model and PrP in a prion disease model. No such evidence has been presented for the use of ATTR in a transthyretin disorder model. And as noted above for the reasons detailed above that substitution of one protein for another, as an immunogenic agent is unpredictable. Further, Goldsteins *et al.* (March 1999) "Exposure of cryptic epitopes on transthyretin only in amyloid and in amyloidogenic mutants." PNAS **96**: 3108-3113 teaches that transthyretin is a transport protein in plasma for thyroid hormone which has the potential to form amyloid fibrils and two major clinical conditions are known. Most of the TTR-associated disorders are linked to point mutations of which more than 50 are known in the art. Therefore it is not clear to the skilled artisan to which mutation the present claims are drawn or to which epitope the antibodies must be raised against as to be considered a "therapeutic" immune response.

24. The issue in "**(g)**" is *moot* in view of Applicant's current amendment of claim 11.

25. The issue in "**(h)**" is *maintained* for the reasons discussed above. The references and data concerning Ab and PrP are compelling although each was done in an art-accepted model for each particular disorder. This is not the case with ATTR. Therefore, no nexus between ATTR immunizations, whether passive or active, has been established with a transthyretin disorder.

26. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of practicing the claimed method as a means of prevention when only treatment was demonstrated as exemplified in the references herein.

27. The rejection of claims **11-19** and **21-25** under 35 U.S.C. §112 ¶1 is maintained.

28. The rejection of claims 11-25 under provisional obvious-type non-statutory double patenting as set forth at pp. 11-13 ¶21-28 in the previous Office Action (Paper No. 9, 21 November 2002) is *maintained.*

New Rejections

Provisional Non-Statutory Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
>
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
>
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

29. Claims **11-19** and **21-25** are provisionally rejected under the judicially created doctrine of double patenting as being unpatentable over claims **11, 14-16, 19,** and **21-25** of copending Application No. **09/585817**, claims **11, 15, 18-19,** and **21-25** of copending Application No.

09/724567, and claims **11, 14, 16, 18-19, 21-25,** and **58** of copending Application No. **09/724953**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the listed claims of each of the above co-pending applications are drawn to a species (PrP, Aβ, synuclein) of the genus (amyloid components) claimed by the instant application 09/724575. Thus the instant claims not only reiterate these species and others but the genus as claimed encompasses them. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Summary

30. No claims are allowed.

31. The following articles, patents, and published patent applications were found by the Examiner during the prior art search and are here made of note:

a. US 2002/0160394 A1 (31 October 2002) Wu

b. Tal *et al.* (2003) "Complete Freund's Adjuvant Immunization Prolongs Survival in Experimental Prion Disease in Mice." Journal of Neuroscience Research **71**: 286-290

c. Wisniewski *et al.* (2002) "Therapeutics in Alzheimer's and Prion Diseases." Biochemical Society Transactions **30**(4): 574-578

32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
July 14, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER